

## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING  
DOCUMENT TRANSMITTED

To:

United States Patent and Trademark  
Office  
Washington, D.C.

in its capacity as elected Office

Date of mailing:

05 April 1994 (05.04.94)

International application No.:

PCT/US92/11214

International filing date:

18 December 1992 (18.12.92)

Applicant:

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES et al

The International Bureau transmits herewith the following documents and number thereof:

\_\_\_\_\_ copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

M. Abidine

Telephone No.: (41-22) 730.91.11

## PATENT COOPERATION TREATY

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## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
Washington, D.C.

in its capacity as elected Office

Date of mailing:

14 October 1993 (14.10.93)

International application No.:

PCT/US92/11214

Applicant's or agent's file reference:

FP41 9359

International filing date:

18 December 1992 (18.12.92)

Priority date:

18 December 1991 (18.12.91)

Applicant:

EVANS, Ronald, M. et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

12 July 1993 (12.07.93)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

B. Morariu

Telephone No.: (41-22) 730.91.11

# PATENT COOPERATION TREATY

## PCT

31 MAR 1994

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FP41 9359	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US92/11214	International filing date (day/month/year) 18 DECEMBER 1992	Priority date (day/month/year) 18 DECEMBER 1991
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE SALK INSTITUTE FOR BIOLOGICAL STUDIES		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority.

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  12 JULY 1993	Date of completion of this report  10 March 1994
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  JON P. WEBER, PH.D. <i>Bill Warden for</i>
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0196

BEST AVAILABLE COPY

**I. Basis of the report**

1. This report has been drawn on the basis of:

- ☐ the international application as originally filed.
- ☒ the description, pages (See Attached) , as originally filed.  
pages \_\_\_\_\_ , filed with the demand.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.
- ☒ the claims, pages (See Attached) , as originally filed.  
pages \_\_\_\_\_ , as amended under Article 19.  
pages \_\_\_\_\_ , filed with the demand.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.
- ☒ the drawings, sheets/fig (See Attached) , as originally filed.  
sheets/fig \_\_\_\_\_ , filed with the demand.  
sheets/fig \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
sheets/fig \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of: pages: NONE  
sheets of drawings/figures No.: NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below.

4. Additional observations, if necessary:

**II. Priority**

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit requested:
- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purpose of this report, the international filing date indicated above is considered to be the relevant date.

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3 and 5-25

because:

☒ the said following application, or the said claim Nos. 1-3 and 5-25 relate to the following subject matter which does not require international preliminary examination (*specify*).

Claims 1-3 and 5-25 either partially or completely are directed to a method of treatment of human/animal body.

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. \_ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. \_ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-3 AND 5-25.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☒ restricted the claims. (See Supplemental Sheet)
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1 not to invite the applicant to restrict or pay additional fees, for the following reasons:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 4, 26 and 28-29.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>4, 26</u>	YES
	Claims <u>28-29</u>	NO
Inventive Step (IS)	Claims <u>4, 26</u>	YES
	Claims <u>28-29</u>	NO
Industrial Applicability (IA)	Claims <u>4, 26, 28-29</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS****NEW CITATIONS**

US, A, 3,984,544 (CASMER ET AL.) 05 OCTOBER 1976, see column 2, lines 25-39, for example and elsewhere in the disclosure.

GB, A, 2,208,601 (GROLLIER) 12 APRIL 1989, see page 6, second full paragraph.

FR, A, 2,641,184 (GROLLIER ET AL.) 06 JULY 1988, see page 10, lines 20-33, for example.

J. AM. CHEM. SOC., Volume 102, issued 1980, H. Akita et al., "Nonbleachable Rhodopsins Retaining the Full Natural Chromophore", pages 6370-6372, see Table 1, and compounds 3, 17, V.

PHOTOBIOCHEM. PHOTOBIOPHYS., Vol. 13, issued 1986, F. Derguini et al., "Synthetic Rhodopsin Analogs", pages 259-283, see compounds 9-11, 18, 23-27, 39-40, 44, 46-48, and 58-59.

SCIENCE, Vol. 258, issued 18 December 1992, J. Lehmann et al., "Retinoids Selective for Retinoid X Receptor Response Pathways", pages 1944-1946, see entire document (cited in Certain Observations).

**EXPLANATIONS**

Claims 28-29 lack novelty under PCT Article 33(2) as being clearly anticipated by Casmer et al. ('544). Casmer et al. disclose 9-cis and 9, 13 dicis-retinoic acid and derivatives of steroids.

Claims 28-29 lack novelty under PCT Article 33(2) as being clearly anticipated by Grollier ('601) or Grollier (FR 2,619,309). Grollier discloses 9-cis and 9, 13-dicis retinoic acid and derivatives. Grollier (FR 2,619,309) is the French language equivalent cited in the International Search Report.

Claims 28-29 lack novelty under PCT Article 33(2) as being (Continued on Supplemental Sheet.)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US92/11214

## VI. Certain documents cited

### 1. Certain published documents

<u>Application No. Patent No.</u>	<u>Publication Date (day/month/year)</u>	<u>Filing Date (day/month/year)</u>	<u>Priority date (valid claim) (day/month/year)</u>
US, A 5,192,534	09 MARCH 1993	13 FEBRUARY 1992	30 DECEMBER 1988

### 2. Non-written disclosures

<u>Kind of non-written disclosure</u>	<u>Date of non-written disclosure (day/month/year)</u>	<u>Date of written disclosure referring to non-written disclosure (day/month/year)</u>

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 4, 26 and 28 are objected to as indefinite under PCT Article 6 for lack of clarity.

Claims 4 and 26 depend from non-examined claims and should properly be recited in independent form.

Claim 28 shows structures of rings interconnected without clearly indicating the nature of the interconnections, the site of the interconnection, etc. This renders the metes and bounds of the claim so unclear that no meaningful interpretation of the structures can be rendered.

Claims 4, 26 and 28-29 are objected to under PCT Article 6 because it is not fully supported by the disclosure.

Applicants have disclosed 9-cis retinoic acid as the endogenous ligand for RXRs as opposed to RARs.

The mere recitation in the specification of the broad inventive concept does not necessarily provide a sufficient basis for claiming it. Operability and utility must be demonstrated by representative examples. The standard for enablement and complete and full disclosure is not the same as that for establishing anticipation. With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility.

In the present case applicant is making multiple substitutions which include: multiple rings of indefinite size and connectivity; large numbers of different side groups of different sizes and physical properties. In light of the unpredictable nature of the receptor/ligand binding art and the large number of substitutions in the claimed invention, additional examples should have been provided in order to better demonstrate the invention's utility. A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim will possess the alleged utility.

For example, Lehmann et al. (1992) examined several analogs of 9-cis retinoic acid with mixed results in effecting RARs or RXRs. Lehmann et al. generated minimum-energy conformations of their analogs by molecular modeling and even still those features which make a good analog are not clear except in broad generalizations at specific sites (page 1945, last column). Small changes in the size or properties of the side groups appear to make significant changes in receptor binding and the ability to transfect cells. It is also apparent that the effects depend on whether homodimer RAR, RXR or heterodimer RXR/RAR receptors are sensitive to the ligand (Figure 4).

(Continued on Supplemental Sheet.)

**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box [No.]: I - VIII

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:  
IPC (5): A61K 31/07, 31/505; C07C 403/20; C07D 213/00, 221/18, 221/22, 249/14, 249/16; C12N 5/00  
U.S. CL.: 435/240.1, 280; 514/256, 725, 880; 546/1, 26, 268, 285

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description,  
pages, 1-52, as originally filed.  
pages, NONE, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the claims,  
pages, 53-73 and 75-78, as originally filed.  
pages, NONE, as amended under Article 19.  
pages, 74, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the drawings,  
sheets, NONE, as originally filed.  
sheets, NONE, filed with the demand.  
and additional amendments:  
Sheets 1-6, filed with the letter of 18 FEBRUARY 1993.

**IV. LACK OF UNITY OF INVENTION:**

1. This response is made to a telephone Lack of Unity requirement (see telephone memorandum attached hereto or attached to a prior Written Report).

Group I, claims 4, 26 and 28-29 drawn to a first method of using retinoids in vitro to modulate processes, a first method of making retinoids in vivo, and the retinoids per se.

Group II, claim 27, drawn to a second method of making retinoids in vitro.

The inventions listed as Groups I and II do not meet the requirements for Unity of Invention for the following reasons: Group II is clearly an alternative method of making the retinoids of Group I, being in vitro as opposed to in vivo. The methods are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept. Note that PCT Rule 13 does not provide for multiple methods within a single application.

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

clearly anticipated by Grollier et al. ('184).

Grollier et al. disclose 9-cis and 9, 13-dicis retinoic acid and derivatives. Grollier (US, A, 5,192,534) is the English language equivalent.

Claims 28-29 lack novelty under PCT Article 33(2) as being clearly anticipated by Akita et al.

Akita et al. disclose 9-cis and 9,11-dicis retinal analogs, some of which are "locked" into the cis configuration by the presence of a ring at carbons 10-13.

Claims 28-29 lack novelty under PCT Article 33(2) as being clearly anticipated by Derguini et al.  
Derguini et al. disclose a variety of 9-cis retinal derivatives.

Claims 28-29 lack an inventive step under PCT Article 33(3) as being obvious over Akita et al. in view of Derguini et al., Casmer et al. and Grollier et al.

Akita et al. disclose the concept of locking the cis configuration of 9-cis and 9, 11-dicis retinoic acid analogs by use of a ring. Akita et al. lacks all of the rings of the instant application.

**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box [No.]: I - VIII

Derguini et al. and Grollier et al. disclose a wide variety of 9-cis and 9, 13-dicis retinoic acid and retinal derivatives.

It would have been prima facie obvious to a person of ordinary skill in the art that other ring structures similar to that disclosed by Akita et al. would also serve to "lock" the 9-cis configuration of retinoic acid, retinal and derivatives as disclosed by Derguini et al. and Grollier et al.

Claims 4 and 26 meet the criteria set out in PCT Article 33(2)-(4) for novelty, inventive step and industrial applicability.

None of the cited references anticipates or renders obvious the method of use of the claimed compounds to regulate in vitro cellular proliferation.

Claims 28-29 meet the criteria set out in PCT Article 33(4) for industrial applicability.

The claimed process may have utility in cell culture technology.

**VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):**

Claim 4 does not appear to have support for in vitro limb morphogenesis.

The breadth of the claims is not commensurate with the enabling disclosure.

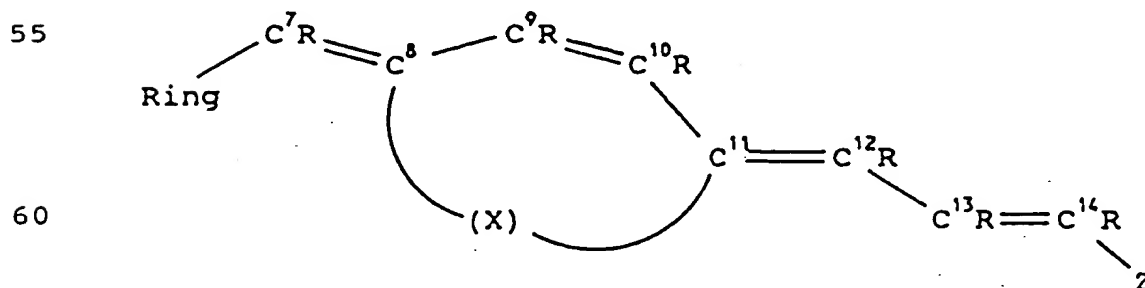
JUL 12 JUL 1993

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above], thioesters of thioalkyl groups  
 $[-(CR'_2)_n-S-CS-R']$ , wherein  $R'$  and  $n$  are as defined  
 above], aminoalkyl  $[-(CR'_2)_n-NR'_2]$ , wherein  $R'$  and  
 40  $n$  are as defined above], N-acyl aminoalkyl  
 $[-(CR'_2)_n-NR'-CO-R'']$ , wherein  $R'$  and  $n$  are as  
 defined above and  $R''$  is a lower alkyl or benzyl],  
 carbamate  $[-(CR'_2)_n-NR'-CO-OR']$  or  
 $-(CR'_2)_n-O-CO-NR'_2$ , wherein  $R'$  and  $n$  are as  
 45 defined above]; and

each  $R$  is independently selected from H,  
 halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
 thioalkoxy, amino, or any of the Z substituents,  
 with the proviso that Structure A is not  
 50 9-cis-retinoic acid or 9,13-dicis-retinoic acid;  
 or

any two or more of the  $R$  groups can be  
 linked to one another to form one or more ring  
 structures;



Structure I;

wherein:

"Ring", Z and R are as defined above;  
 65 X is  $-\{ (CR_2)_x - X' - (CR_2)_y \}-$ ,  
 $X'$  is selected from  $-O-$ , carbonyl,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , thiocarbonyl,  $-NR''-$ , or  $-CR_2-$ ,  
 $R''$  is hydrogen, alkyl, hydroxy, thiol, or alkoxy  
 acyl;  
 70 x is 0, 1 or 2,  
 y is 0, 1, or 2, and  
 $x + y \leq 2$ ;

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only	
PCT/US 92/11214	
International Application No.	
International Filing Date 18 DEC 1992	
PCT INTERNATIONAL APPLICATION RO/US	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) FP41 9359	

Box No. I TITLE OF INVENTION	
MEANS FOR THE MODULATION OF PROCESSES MEDIATED BY RETINOID RECEPTORS AND COMPOUNDS USEFUL THEREFOR	
Box No. II APPLICANT	
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	<input type="checkbox"/> This person is also inventor.
THE SALK INSTITUTE FOR BIOLOGICAL STUDIES 10010 North Torrey Pines Road La Jolla, California 92037 United States of America	Telephone No. (619) 453-4100 Facsimile No. (619) 450-0509 Teleprinter No.
State (i.e. country) of nationality: US	State (i.e. country) of residence: US
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS	
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	This person is:
BAYLOR COLLEGE OF MEDICINE 1 Baylor Plaza Houston, Texas 77030 United States of America	<input checked="" type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: US	State (i.e. country) of residence: US
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)	This person is:
LIGAND PHARMACEUTICALS, INC. 9393 Towne Centre Drive, Suite 100 San Diego, California 92121 United States of America	<input checked="" type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality: US	State (i.e. country) of residence: US
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS			
<i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>			
<b>Name and address:</b> <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>  EVANS, Ronald M. 8615 La Jolla Scenic Road La Jolla, California 92037 United States of America		<b>This person is:</b> <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
<b>State (i.e. country) of nationality:</b> US		<b>State (i.e. country) of residence:</b> US	
<b>This person is applicant for the purposes of:</b> <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<b>Name and address:</b> <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>  MANGELSDORF, David J. 4771 Seaford Place San Diego, California 92117 United States of America		<b>This person is:</b> <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
<b>State (i.e. country) of nationality:</b> US		<b>State (i.e. country) of residence:</b> US	
<b>This person is applicant for the purposes of:</b> <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<b>Name and address:</b> <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>  HEYMAN, Richard A. 147 Honeycomb Court Encinitas, California 92024 United States of America		<b>This person is:</b> <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
<b>State (i.e. country) of nationality:</b> US		<b>State (i.e. country) of residence:</b> US	
<b>This person is applicant for the purposes of:</b> <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<b>Name and address:</b> <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i>  BOEHM, Marcus F. 4007 Everts Street, 4J San Diego, California 92109 United States of America		<b>This person is:</b> <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
<b>State (i.e. country) of nationality:</b> US		<b>State (i.e. country) of residence:</b> US	
<b>This person is applicant for the purposes of:</b> <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.			

## Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: (Family name followed by given name; for a legal entry, full official designation. The address must include postal code and name of country.)

EICHELE, Gregor  
2030 Swift Boulevard  
Houston, Texas 77030  
United States of America

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:  
CHState (i.e. country) of residence:  
USThis person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entry, full official designation. The address must include postal code and name of country.)

THALLER, Christina  
2030 Swift Boulevard  
Houston, Texas 77030  
United States of America

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:  
FRState (i.e. country) of residence:  
USThis person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entry, full official designation. The address must include postal code and name of country.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entry, full official designation. The address must include postal code and name of country.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No. VI PRIORITY CLAIM**Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country (in which, or for which, the application was filed)	Filing Date (day/month/year)	Application No.	Office of filing (only for regional or international application)
(1) US	(18.12.91) 18 December 1991	07/809,980	
(2)			
(3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to transmit to the International Bureau a certified copy of the earlier application(s) identified above at item(s) : 1**Box No. VII EARLIER SEARCH**

Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:

Country (or regional Office): Date (day/month/year): Number:

**Box No. VIII CHECK LIST**

This international application contains the following number of sheets:

1. request : 5 sheets  
 2. description : 52 sheets  
 3. claims : 26 sheets  
 4. abstract : 1 sheets  
 5. drawings : 6 sheets

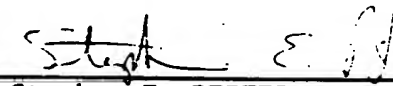
Total : 90 sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney  
 2. ☐ copy of general power of attorney  
 3. ☐ statement explaining lack of signature  
 4. ☐ priority document(s) (specify):  
 5. ☒ fee calculation sheet  
 6. ☐ separate indications concerning deposited microorganisms  
 7. ☐ nucleotide and/or amino acid sequence listing  
 8. ☐ other (specify):

Figure No. None of the drawings (if any) should accompany the abstract when it is published.**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

  
 - Stephen E. REITER  
 Reg. No. 31,192

For receiving Office use only

1. Date of actual receipt of the purported international application:	13 Rec'd PCT/P 18 DEC 1992	2. Drawings: <input checked="" type="checkbox"/> received <input type="checkbox"/> not received
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority specified by the applicant: ISA / Ep	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

28 MAR 1993

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s) :

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES  
10010 North Torrey Pines Road  
La Jolla, California 92037  
United States of America

hereby appoint(s) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

REITER, Stephen E.  
PRETTY, SCHROEDER, BRUEGGEMANN & CLARK  
444 South Flower Street  
Suite 2000  
Los Angeles, California 90071  
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

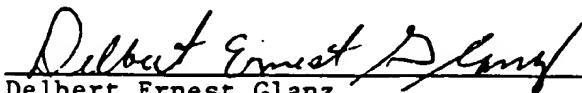
in connection with any and all international applications filed by the undersigned with the following Office

United States

as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) (where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power):

  
Delbert Ernest Glanz  
Executive Vice President  
THE SALK INSTITUTE FOR  
BIOLOGICAL STUDIES

Date: January 21, 1993

RG/US

23 MAR 1993

IN THE UNITED STATES RECEIVING OFFICE

In re International Application of )  
THE SALK INSTITUTE FOR BIOLOGICAL )  
STUDIES )  
BAYLOR COLLEGE OF MEDICINE )  
LIGAND PHARMACEUTICALS, INC. )  
Application No.: PCT US92/11214 )  
Filed: December 18, 1992 )  
Entitled: MEANS FOR THE MODULATION OF )  
PROCESSES MEDIATED BY RETINOID )  
RECEPTORS AND COMPOUNDS USEFUL )  
THEREFOR )

POWER OF ATTORNEY

BOX PCT  
Hon. Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

We hereby appoint the following attorneys to prosecute the above-identified application and any subsequent application based on the disclosure of this application and to transact all business in the PCT office connected therewith:

STEPHEN E. REITER, Registration No. 31,192,  
JAMES R. BRUEGGEMANN, Registration No. 28,286; ROBERT A.  
SCHROEDER, Registration No. 25,393; LAURENCE H. PRETTY,  
Registration No. 25,312; and GARY A. CLARK, Registration  
No. 28,060. Direct all telephone calls to Stephen E.  
Reiter at telephone no. (619) 546-4737.

Address all Correspondence to:

STEPHEN E. REITER  
Pretty, Schroeder, Brueggemann & Clark  
444 South Flower Street, Suite 2000  
Los Angeles, California 90071

LIGAND PHARMACEUTICALS, INC.

Date 3-1-93

By William L. Respass  
William L. Respass

Title: Vice President and  
General counsel

IN THE UNITED STATES RECEIVING OFFICE

In re International Application of )  
THE SALK INSTITUTE FOR BIOLOGICAL )  
STUDIES )  
BAYLOR COLLEGE OF MEDICINE )  
LIGAND PHARMACEUTICALS, INC. )  
Application No.: PCT US92/11214 )  
Filed: December 18, 1992 )  
Entitled: MEANS FOR THE MODULATION OF )  
PROCESSES MEDIATED BY RETINOID )  
RECEPTORS AND COMPOUNDS USEFUL )  
THEREFOR )

POWER OF ATTORNEY

BOX PCT  
Hon. Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir: ✓

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STEPHEN E. REITER, Registration No. 31,192,  
JAMES R. BRUEGGEMANN, Registration No. 28,286; ROBERT A.  
SCHROEDER, Registration No. 25,393; LAURENCE H. PRETTY,  
Registration No. 25,312; and GARY A. CLARK, Registration  
No. 28,060. Direct all telephone calls to Stephen E.  
Reiter at telephone no. (619) 546-4737.

Address all Correspondence to:

STEPHEN E. REITER  
Pretty, Schroeder, Brueggemann & Clark  
444 South Flower Street, Suite 2000  
Los Angeles, California 90071

BAYLOR COLLEGE OF MEDICINE

Date March 1, 1993

By Samuel Crocker  
Samuel Crocker

Title: Vice President  
for Legal Affairs

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/ ☒ **agent** ☐ **common representative** of the applicant(s) before the competent International Authorities as:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

REITER, Stephen E.  
Pretty, Schroeder, Brueggemann & Clark  
444 South Flower Street  
Suite 2000  
Los Angeles, California 90071

**United States of America**

Telephone No.

(619) 546-4737

Facsimile No.

(619) 546-9392

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

**Regional Patent**

☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FR France, GB United Kingdom, GR Greece, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ **OA OAPI Patent:** Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Gabon, Guinea, Mali, Mauritania, Senegal, Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

**National Patent** (if other kind of protection or treatment desired, specify on dotted line):

☐ AT Austria

☒ AU Australia

☐ BB Barbados

☐ BG Bulgaria

☐ BR Brazil

☒ CA Canada

☐ CH and LI Switzerland and Liechtenstein

☐ CS Czechoslovakia

☐ DE Germany

☐ DK Denmark

☐ ES Spain

☐ FI Finland

☐ GB United Kingdom

☐ HU Hungary

☒ JP Japan

☐ KP Democratic People's Republic of Korea

☐ KR Republic of Korea

☐ LK Sri Lanka

☐ LU Luxembourg

☐ MG Madagascar

☐ MN Mongolia

☐ MW Malawi

☐ NL Netherlands

☐ NO Norway

☐ PL Poland

☐ RO Romania

☐ RU Russian Federation

☐ SD Sudan

☐ SE Sweden

☒ US United States of America CIP

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☐

☐

☐

☐

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of \_\_\_\_\_

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

**Supplemental Box***If the Supplemental Box is not used, this sheet need not be included in the request.***Use this box in the following cases:****1. If, in any of the Boxes, the space is insufficient to furnish all the information:***in particular:*

- (i) if more than three persons are involved as applicants and/or inventors and no "continuation sheet" is available;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," "certificate of addition," or "inventor's certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part";
- (vi) if there are more than three earlier applications whose priority is claimed;

*in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;**in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;**in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State or States (and/or, where applicable, European or OAPI patent) for the purposes of which the named person is applicant;**in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State or States (and/or, where applicable, European or OAPI patent) for the purposes of which the named person is inventor;**in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;**in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;**in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.***2. If the applicants claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:***in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.*Continuation of Box No. V

United States of America Application No. 07/809,980, filed 18 December 1991  
(18.12.91)

**PCT****FEE CALCULATION SHEET**  
**Annex to the Request**

For receiving Office use only

**PCT/US 92/ 11214**

International application No.

**18 DEC 1992**

Date stamp of the receiving Office

Applicant's or agent's  
file reference

FP41 9359

Applicant

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES, BAYLOR COLLEGE  
OF MEDICINE AND LIGAND PHARMACEUTICALS, INC.**CALCULATION OF PRESCRIBED FEES**1. TRANSMITTAL FEE . . . . . 200 ☐ T2. SEARCH FEE . . . . . 1,635 ☐ SInternational search to be carried out by EPO  
(If two or more International Searching Authorities are competent in relation to the international  
application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

**Basic Fee**The international application contains 90 sheets.first 30 sheets . . . . . 525 ☐ b<sub>1</sub>60 x 10 = 600 ☐ b<sub>2</sub>  
remaining sheets additional amountAdd amounts entered at b<sub>1</sub> and b<sub>2</sub>  
and enter total at B . . . . . 1,125 ☐ B**Designation Fee**5 x 127 = 635 ☐ D  
number of designations amount of designation fee(If that total exceeds the figure which corresponds to the amount of the  
designation fee multiplied by ten, enter the latter figure in box D.)Add amounts entered at B and D and enter total at I . . . . . 1,760 ☐ I4. FEE FOR PRIORITY DOCUMENT . . . . . 12 ☐ P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P.  
and enter total in the TOTAL box . . . . .

3,607

TOTAL

200.001635.00593.00720.001313.00720.002033.0012.003880.00☐ The designation fee is not paid at this time.**MODE OF PAYMENT**☒ authorization to charge  
deposit account (see below)☐ bank draft☐ coupons☒ cheque☐ cash☐ other (specify):☐ postal money order☐ revenue stamps**DEPOSIT ACCOUNT AUTHORIZATION**The RO/ US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my  
deposit account.☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International  
Bureau of WIPO to my deposit account.

16-2460

Deposit Account Number

18 December 1992

Date (day/month/year)

Signature Stephen E. Reiter

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>FP41 9359</b>	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US92/11214</b>	International filing date (day/month/year) <b>18/12/92</b>	(Earliest) Priority Date (day/month/year) <b>18/12/91</b>
Applicant <b>THE SALK INSTITUTE FOR BIOLOGICAL STUDIES et al.</b>		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract, ☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:  
 Figure No. \_\_\_\_\_ ☐ as suggested by the applicant. ☒ None of the figures.  
☐ because the applicant failed to suggest a figure.  
☐ because this figure better characterizes the invention.

**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box [No.]: I - VIII

Sheet 10

Derguini et al. and Grollier et al. disclose a wide variety of 9-cis and 9, 13-dicis retinoic acid and retinal derivatives.

It would have been prima facie obvious to a person of ordinary skill in the art that other ring structures similar to that disclosed by Akita et al. would also serve to "lock" the 9-cis configuration of retinoic acid, retinal and derivatives as disclosed by Derguini et al. and Grollier et al.

Claims 4 and 26 meet the criteria set out in PCT Article 33(2)-(4) for novelty, inventive step and industrial applicability.

None of the cited references anticipates or renders obvious the method of use of the claimed compounds to regulate in vitro cellular proliferation.

Claims 28-29 meet the criteria set out in PCT Article 33(4) for industrial applicability.

The claimed process may have utility in cell culture technology.

**VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):**

Claim 4 does not appear to have support for in vitro limb morphogenesis.

The breadth of the claims is not commensurate with the enabling disclosure.

## I. INTERNATIONAL SEARCH REPORT

PCT/US 92/11214

International Application No.

## I. CLASSIFICATION OF SUBJECT MATTER

Several classification symbols apply, indicate all<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC  
 Int.Cl. 5 A61K31/07; C07C403/20

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.Cl. 5	C12N ; C07C ; C12P ; A61K

Documentation Searched other than Minimum Documentation  
 to the extent that such Documents are included in the Fields Searched<sup>8</sup>

III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 376 821 (L'OREAL, FR) 4 July 1990 See the whole document, especially page 7, line 16, the claims ---	28,29
X	FR,A,2 619 309 (L'OREAL, FR) 17 February 1989 See the whole document, especially page 7 line 35, the claims ---	28,29
P,X	JP,A,4 253 934 (NISSHIN FLOUR MILLING CO, LTD) 9 September 1992 see the whole document --- -/-	28-29

<sup>9</sup> Special categories of cited documents: <sup>10</sup><sup>10</sup> "A" document defining the general state of the art which is not considered to be of particular relevance<sup>10</sup> "E" earlier document but published on or after the international filing date<sup>10</sup> "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<sup>10</sup> "O" document referring to an oral disclosure, use, exhibition or other means<sup>10</sup> "P" document published prior to the international filing date but later than the priority date claimed<sup>10</sup> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<sup>10</sup> "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step<sup>10</sup> "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.<sup>10</sup> "A" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search 10 MAY 1993	Date of Mailing of this International Search Report 25. 05. 93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer S.A. NAUCHE

International Application No.

PCT/US 92/11214

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	<p>NATURE. vol. 355, 23 January 1992, LONDON GB pages 359 - 361 Levin AA;Sturzenbecker LJ;Kazmer S;Bosakowski T;Huselson C;Allenby G;Speck J;Kratzeisen C;Rosenberger M;Lovey A;et al; '9-cis retinoic acid stereoisomer binds and activates the nuclear receptor RXR alpha.' see the whole document</p> <p>---</p>	1-22
P,X	<p>CURRENT BIOLOGY vol. 2, no. 6, June 1992, pages 293 - 295 Laudet, V. et al.; 'Nuclear receptors : Flexible friends' see the whole document</p> <p>---</p>	1-22
P,X	<p>CELL vol. 68, no. 2, 24 January 1992, CAMBRIDGE, MA US pages 397 - 406 Heyman RA;Mangelsdorf DJ;Dyck JA;Stein RB;Eichele G;Evans RM;Thaller C; '9-cis retinoic acid is a high affinity ligand for the retinoid X receptor.' see the whole document</p> <p>---</p>	1-22
A	<p>THE JOURNAL OF CELL BIOLOGY vol. 99, no. 4, October 1984, NEW YORK, USA page 153A Yen, A. et al.; 'Retinoic acid induced HL-60 Myeloid differentiation sensitivity of early and late events to Cis-Trans isomerisation.' See abstract 563</p> <p>---</p>	1-22
A	<p>LEUKEMIA RESEARCH vol. 10, no. 6, 1986, OXFORD, GB pages 619 - 629 YEN, A. ET AL.; 'Retinoic acid induced HL-60 myeloid differentiation : dependence of early and late events on isomeric structure'</p> <p>-----</p>	1-22

## INTERNATIONAL SEARCH REPORT

International application No.

CT/US 92/ 11214

**Box I (Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet))**

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1-3, 6-24 all partially, and claims 5, 25 both completely, are directed to a method of treatment of the human/animal body (Rule 39.1(iv)PCT) the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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